

Performing a high quality examination in patients with Barrett's oesophagus

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Barretts oesophagus – a precursor lesion to adenocarcinoma

Barretts oesophagus (BE) remains the only identified precursor lesion to oesophageal adenocarcinoma. Various definitions exist for Barrett's oesophagus; but all require the replacement of the normal squamous oesophageal mucosa above the gastro-intestinal junction (GOJ), with endoscopically and histologically confirmed metaplastic columnar epithelium¹⁰. Both the UK and European guidelines additionally state that this metaplasia should be identified more than 1cm above the GOJ^{11,12}. The asymptomatic nature of BE means that it is often incidentally detected on routine endoscopy and so quantifying its presence in a general population is complex – with figures ranging from 1-2%²⁰ in some studies to 5.6%¹³ in a large US model. In a cohort of white, US males with chronic gastro-oesophageal reflux disease this figure rises to just less than 14%.

Barrett's oesophagus is of clinical significance. Although it is largely asymptomatic, it is a recognised precursor lesion to OAC, and should prompt endoscopic surveillance. There is a well established linear progression from non-dysplastic BE, through to low grade dysplasia (LGD) and high grade dysplasia (HGD), with an increasing annual risk of progression to OAC of 0.4%, 8.8% and 19% respectively^{1,2,3}. The incidence of OAC in the western world continues to increase () and remains a cancer with a dismal prognosis. The 5-year mortality of OAC remains low at 17.9%¹⁷, but is particularly poor for patients presenting late in the disease course³⁰. Patients with early neoplasia, confined to the mucosa, are potential candidates for endoscopically delivered therapy, which has impressive cure rates of over 90%²⁵, without the attendant morbidity and mortality of surgical management options. Furthermore, clinicians now have a number of endoscopically delivered therapies to offer patients who would traditionally have been offered only palliative therapies having been considered not fit enough to withstand such major surgery. Clinicians have therefore directed considerable efforts towards improving the detection of dysplasia and early neoplasia within BE segments at an earlier stage, predominantly through endoscopic surveillance programs.

The need for effective BE surveillance

The current paradigm for the surveillance of BE patients involves the interval endoscopic assessment of their BE segment in order to identify early neoplastic lesions while they remain amenable to endoscopic therapy. The current gold standard for endoscopic surveillance is the Seattle protocol²⁸, beginning with a careful assessment of the oesophagus from the gastro-oesophageal junction (GOJ) to the proximal squamo-columnar junction, looking for features of early cancer. Accurate identification of the GOJ is essential to ensure that patients with intestinal metaplasia in the cardia, a normal finding in around 20% of people¹⁹, are not labelled as having BE and subjected to unnecessary surveillance endoscopies despite a

minimal risk of progression to OAC. The top of the visible gastric folds should be identified as the anatomical landmark of the GOJ, the position from which measurements of visible columnar tissue should begin. To standardise reporting of both endoscopic and histologic findings in BE patients, the Prague and Paris classifications are used. The Prague classification is a consensus driven, validated reporting criteria that requires endoscopists to detail the location of the top of the gastric folds, the maximal proximal extent of both the circumferential BE segment as well as any tongues or islands²³. Accurate recording of the Prague classification is vital for a number of reasons. First, the length of the Barrett's segment determines the intervals at which patients without evidence of dysplasia should undergo endoscopic surveillance. Second, if dysplastic tissue is identified incidentally on biopsies it provides subsequent endoscopists with a location to which they should give particular focus during future assessments. Lastly, it determines both where endoscopic treatment should be directed and particularly, in the case of patients who have undergone radiofrequency ablation (RFA), where biopsies should be taken from to identify buried, sub-squamous intestinal metaplasia in the macroscopically normal post-treatment oesophagus. Once the initial assessment and measurements have been completed target biopsies are taken from areas that appear macroscopically suspicious for neoplasia. To complete the protocol, endoscopists then take random forceps biopsies across the four quadrants of the oesophageal mucosa, starting at the GOJ and then every two centimetres until the proximal border of the BE segment is reached.

While the Seattle Protocol remains the gold standard, it is not without limitations. Tschanz et al. highlight the susceptibility of the protocol to sampling error. The average BE mucosal surface area is estimated at 14cm², with random forceps biopsies sampling only around 0.5cm² of this area - representing just 3.5% of the total surface area¹⁵. Early BE dysplasia and neoplasia is often highly focal and easily missed with this sampling technique. Moreover, studies have also demonstrated that compliance with the protocol is often poor and worsens with longer segments – with sensitivity for dysplasia detection ranging widely from 28-85%²⁹. A large meta-analysis demonstrated that a sobering 16.4-36.8% of OAC is diagnosed within one year following an index surveillance endoscopy¹⁶. This again serves to highlight to clinicians undertaking BE surveillance of the fact that random sampling is not a replacement for a thorough and careful endoscopic examination.

Identifying early neoplastic lesions in Barrett's oesophagus

Endoscopists should pay careful attention to subtle mucosal and vascular features visible within the BE segment during their evaluation. There are a number of classification systems validated in the various imaging modalities available to endoscopists; all typically stratify lesions as dysplastic or non dysplastic based on mucosal or vascular patterns. The BING group proposed a simplified MV classification which has been validated for use with narrow band imaging (NBI), a similar classification has been developed for use with the iScan Optical Enhancement (OE) imaging system. Normal BE mucosa should have a regular pattern of gyriform folds and pits, consistent with the appearance of healthy intestinal columnar tissue. The microvasculature may not always be visible, but if observed vessels should appear ordered, not dilated or branching and should follow the pattern of folds between pits. The presence of disordered pit patterns, or nodularity with associated dilation and formation of aberrant vessels should prompt a more focused evaluation and target biopsies by clinicians to improve

dysplasia detection. If areas suspicious for early neoplasia are found, clinicians should record their findings based on the Paris classification²⁴.

How and where to look during Barrett's surveillance endoscopies

The time spent assessing the oesophagus for 'high risk' areas for the presence of early neoplasia also impacts the quality of BE surveillance endoscopies. Clinicians should spend adequate amounts of time thoroughly assessing the mucosa, mucus should be removed and the oesophagus assessed partially insufflated between waves of peristalsis. Subtle lesions can often be missed with over insufflation due to lesions being flattened and can also be missed within folds of an under insufflated oesophagus. Inspection time of the BE mucosa is significantly associated with improved detection of early lesions. Gupta et al. demonstrated that both identification of suspicious lesions and detection rate of HGD/OAC improved with assessments where endoscopists inspected each centimetre of the BE segment for more than one minute (HGD/OAC detection rate 40.2% vs 6.7%)⁹. Clinicians should therefore ensure that they spend time carefully assessing the cleaned BE segment. Endoscopy units should take such findings into account, particularly when planning workflow, as patients undergoing BE surveillance endoscopies may require longer appointment times to be booked to facilitate a more detailed examination. Several studies have also demonstrated a spatial predilection for early BE associated neoplasia which should guide the endoscopists focus during surveillance. Early cancers are more commonly seen on the right wall of the oesophagus within the proximal segment^{4,5,6,7,8} – particular focus should therefore be given to these areas. This is particularly important in longer segments of BE, given that compliance with the Seattle protocol diminishes with longer segment length.

Adjuncts to endoscopic examination – chromoendoscopy and virtual chromoendoscopy

Given the subtle nature of early neoplastic lesions the topical application of dyes may improve the distinction of dysplastic and non dysplastic tissue. Unlike the colon, methylene blue and indigo carmine have demonstrated disappointing results for highlighting Barrett's dysplasia^{26,27}. However, acetic acid (AA) spray applied to the oesophageal mucosa during surveillance endoscopy does have an established use. Following application of a dilute acetic acid solution clinicians should observe the mucosa, which under normal circumstances turns white as surface glycoproteins denature in the acidic pH. This colour change both highlights mucosal patterns more clearly and furthermore, when observed for a period of up to two minutes, allows clinicians to appreciate the premature loss of aceto-whitening in areas of the mucosa. The efficacy of acetic acid chromoendoscopy has been demonstrated in numerous studies. The application of AA has been shown to improve the diagnostic yield of target biopsies by 14.7 fold compared to random biopsies, with a meta analysis by Coletta et al demonstrating a sensitivity and specificity of 92% and 96% respectively¹⁸. Anecdotal issues with acetic acid chromoendoscopy include a lengthened procedure time, an increased propensity for bleeding and ooze post biopsy and the theoretical risk of aspiration of acidic oesophageal contents.

In order to obviate the need for topical application of dyes to the mucosa, with the associated demand on time and resources, several companies have incorporated virtual

chromoendoscopy (VC) systems into their endoscope platforms. The underlying principle of VC is the use of novel optical filters and post-processing technologies, built into the endoscope and operated with toggle buttons by the endoscopist, to enhance mucosal and vascular patterns seen at endoscopic assessment. VC has shown promise in providing endoscopists with enhanced imaging that may serve to improve recognition of early neoplasia and improve the yield of targeted biopsies

Narrow band imaging (Olympus) utilises transmitted light wavelengths in the blue (415nm) and green (540nm) range of the visible light spectrum. These particular wavelengths penetrate the superficial mucosa and serve to enhance pit patterns as well as the microvasculature. Sharma et al demonstrated the potential of NBI as a replacement for AA chromoscopy. Using a simple mucosal and vessel classification system they showed an accuracy of 92%, and sensitivity and specificity of 91% and 93% respectively in the identification of early dysplastic lesions on still images²².

A similar system called iScan (Pentax, Hoya Ltd) has been developed which utilises the transmission of green and blue wavelengths matched to the main absorption spectrum of haemoglobin, again in order to provide enhanced contrast of the mucosal pit patterns and vasculature. Optical enhancement mode (OE) additionally provides more intense transmission of light across the spectrum, in order to keep the oesophagus well illuminated. A recent study showed that compared the current gold standard of HD-WLE, OE improves the detection of early neoplasia. A further improvement was also obtained when OE was used in combination with zoom magnified endoscopy²¹, importantly this study assessed the detection in real time videos of endoscopic surveillance in order to more closely model the clinical application of this technology. Current iterations of iScan OE are not as effective as NBI, but it may be that as experience with the system and refinements of the technology are made available it will prove to be an alternative selection.

While enhanced endoscopic imaging shows great promise for the future, in the majority of studies it still falls short of the current gold standard. The American Society for Gastrointestinal Endoscopy (ASGE) has published thresholds for the preservation and incorporation of valuable endoscopic innovations (PIVI) that require novel technologies to offer per patient sensitivities of $\geq 90\%$, as well as per patient negative predictive values of $\geq 98\%$ and specificities of $\geq 80\%$ in order to replace random biopsies for the detection of dysplasia²². Additionally, most studies to date have either been performed using still images, or have been undertaken in high volume, BE referral centres and as such might not be an accurate reflection of the units where most surveillance endoscopies take place. Furthermore, advanced imaging modalities are not yet widely available so the clinical experience in a broader setting remains limited.

The future of endoscopic surveillance

The endoscopic assessment of BE for early neoplasia is complex and the attainment of high diagnostic accuracy is multifactorial. As the provision of advanced imaging expands, clinicians will have more in their diagnostic toolkit to facilitate neoplasia detection. Modern day endoscopes are now capable of capturing huge amounts of data, with images of up to 1.2 megapixel resolution. Several groups have demonstrated the feasibility of using these high quality images as source data to develop neural networks capable of identifying early neoplasia³¹. Although it remains a technology in its infancy, early work has shown that neural networks are indeed capable of identifying areas deemed high risk for dysplasia on still images

captured at endoscopy. While the sensitivity and accuracy of such systems do not yet match those of experts, with further refinement and acquisition of larger amounts of data, the technology shows great promise. The development of a 'second read' system that could highlight areas that warrant closer attention or target biopsies to exclude neoplasia may improve both dysplasia detection in less experienced endoscopists as well as shifting the gold standard away from random biopsies to a more targeted approach.

Word count (excluding references) - 2216

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